

THE EFFECT OF CORTISONE
AND DESOXYCORTICOSTERONE ON CAPILLARY
PERMEABILITY IN ALLERGIC PATIENTS¹

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The therapeutic importance of cortico-suprarenal hormones in allergic diseases and the demonstrative fact that in this group of affections, capillary permeability is altered, has induced us to test the modifications which this group of hormones might cause on the capillary physiology of allergic patients.

In the extensive range of substances elaborated by the cortex of the suprarenal glands, there exists a group of some, specially effective in the process of gluco-neogenesis, that is to say, they intervene in the formation of sugars starting from non-sugar derivatives. This is the group of corticoids, called glucocorticoids (G-C) whilst the other is specially active in the regulation of the hydric metabolism and of saline substances, particularly sodium and potassium: they form the group of mineral corticoids (M-C).

Although this distinction should be abandoned, not only for clinical, but also for biochemical reasons, it is nevertheless useful on account of its schematic simplicity, so that it is still used by all of us.

Whilst in the first group of these hormones (G-C) we have cortisone or compound E of *Kendall*, in the second group

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(M-C) is found desoxycorticosterone, known also as DOCA (D-C-A).

These two groups of hormones, G.C. and M.C. are in certain aspects opposed to each other.

Glucocorticoides

Mineralcorticoids

Whilst the former inhibit inflammation, the latter are phylogistic. Cortisone and analogous suprarenal hormones lead to an atrophy of the suprarenal cortex; the drug also inhibits the effects caused by overdosage with DCA (periarteritis, arthritis, etc.) in test animals.

Cortisone, as well as DCA, have been employed in the treatment of allergy. DCA was effectually used first by *Finemann* (1) and later by *Cohen* and *Rudolph* (2) who were not able to show the favourable effect of these hormones, which *Finemann* had found.

Since then, it has been used by numerous authors with inconstant results (3, 4, 5, 6, 7, 8, 9, 10).

The final verdict on the use of cortisone has yet to be given. A good summary of the conflicting reports on this new drug is found in the article by *Cooke* (11).

CAPILLARY PERMEABILITY AND CORTICOIDS

The modification of capillary permeability has been studied by many authors, without any general agreement. Thus the results found with reference to DCA are not in close agreement, although the general tendency inclines to the belief that this hormone favours capillary permeability.

Verzar (12) observes that in cats whose suprarenal glands have been extirpated, as in histaminic shock, the number of erythrocytes increases, while the volumetric quantity of plasma diminishes (haemoconcentration).

Seifert and colleagues (13) have shown that hyaluronidase, as well as the DCA cause the permeability of the

articular synovial membrane to increase in the presence of colouring matter. This is checked by the administration of Cortisone.

Similar conclusion were arrived at by *Pettini* and *Fornaro* (14) who, by measuring the quantity of glucose contained in the aqueous humour and the vitreous humour of the rabbit, observed a greater permeability through the action of DCA, checked by ACTH.

Geyer and *Keibl* (15) on the other hand, did not succeed in showing that DCA increased capillary permeability.

Neither did *Hidalgo* and colleagues (16) confirm the work of other investigators, that cortisone, ACTH, suprarenal cortex extracts and hydroxiphenyl-cinchoninic acid had any significant effect in the sense of altering the permeability of the normal articular membrane of rabbits in the presence of phenolsulphonaphthalein.

Cortisone shows similar findings. Whilst a number of authors like *Leopold* and colleagues (17) are of opinion that it does not affect capillary permeability at all, another group of investigators, like *Chambers* and *Sweifach* (18) think that it does so. An insufficiency of the suprarenal cortex, as well as the administration of cortical extracts and even of certain steroids they believe can influence the permeability of the membrane.

In the same way, cortisone as well as the amorphous fraction and the sodium salt of the phosphate ester of 11-desoxycorticosterone each decreased the time required for the glycerol hemolysis of beef cells at all pH levels.

Hyman and *Chambers* (19) have observed that cortical extracts and certain esters "reduce the rate of edema formation in perfused forelegs. The most effective was the 11-desoxycorticosterone. Cortisone was weakly active but slightly greater than that of strophanthin".

More recently *Opsahl* (20, 21, 22) studied the effect of corticosuprarenal insufficiency, as well as that of the administration of cortico-adrenal extracts and steroids on the action of hialuronidase diffusion.

Adrenalectomy in mice causes spreading of India ink, injected into them intradermically, to increase, whilst the injection of cortico-adrenal extracts checks it, in adrenalectomized mice as well as in normal ones.

The same results could be observed in rabbits and more recently, with purer esteroïds, (cortisone) it was noted that its administration inhibits spreading of India ink, diffused with hyaluronidase, other steroids, like testosterone etc. show no such action.

Other authors, (*Winter and Flataker* (23)) have studied this phenomenon with the help of another colouring matter, T-1824. Cortisone injected intramuscularly, inhibits the diffusing action of hyaluronidase, in the presence of the colouring matter, nevertheless its action is not efficacious when injected locally.

According to the opinion of *Seifert, Baeder and Dervinis* (24) these hormonal products act upon the hyaluronate of the synovial membrane, facilitating its permeability.

Nowadays the general opinion is, that cortisone has an antihyaluronidase action (25). Perhaps the measuring of this antihyaluronidasic power would provide another test to evaluate the possible therapeutic action of the products under study.

Nevertheless, *Menkin* (26) holds that the capillary permeability of the skin of rabbits is not altered, either with ACTH or with cortisone, so long as no vehicle or alcohol is extracted from the latter.

In the case of commercial cortisone suspensions it has been observed that capillary permeability increases in the place of the injection, a circumstance which must be borne in mind when the former have to be studied experimentally or clinically.

Armstrong and Irons (27) found that the contents of proteins in a liquid of a scleroderma diminished from 2.5 % to 0.5 % after administration of ACTH.

In addition to *Leopold* and colleagues (18) who find no difference in the speed of appearance of the colouring matter

in the aqueous humor of normal rabbits, to which cortisone had been administered, either by instillation in drops, or else by subconjunctival injection, or introduced into the anterior chamber. *Cook* and *Mac Donald* (28) confirm these results, utilizing the technique standardized by *Amsler* and *Huber* who showed that the permeability of the aqueous-blood barrier to fluoresceine is not affected by a local or general administration of cortisone. Later on, *Cook* and *Mac Donald* extended their experiments to the human eye, with active inflammation. It appears that although the drug does not act upon capillary permeability when normal, it does on pathologic conditions bringing them back to a normal state.

CAPILLARY PERMEABILITY IN ANAPHYLAXIS AND ALLERGY

We thus see that the literature referring to the influence of DCA and cortisone upon the capillary permeability, is not only scarce, but also that the conclusion reached by different authors are not conclusive and disagree.

When reviewing the literature on the relationship of capillary permeability in allergy, we find very little written. This is truly amazing when it is remembered that the entire problem of allergy turns on histamine and histamine-like substances, which greatly modify permeability.

Manwaring (29) is likewise of the opinion that the increase in capillary permeability in allergy must be the most important phenomenon as it puts into play the entire reactions of allergy.

Capillary permeability can be studied very well in relation to anaphylaxis by the "Phenomenon of Arthus" and also with local anaphylaxis. (Intradermal-reaction brought about with the antigen that has previously been made sensitized to the skin). With one and the other proceeding an increase in capillary permeability in anaphylaxis has been demonstrated.

Lange (30) by means of an apparatus, the dermofluoro-

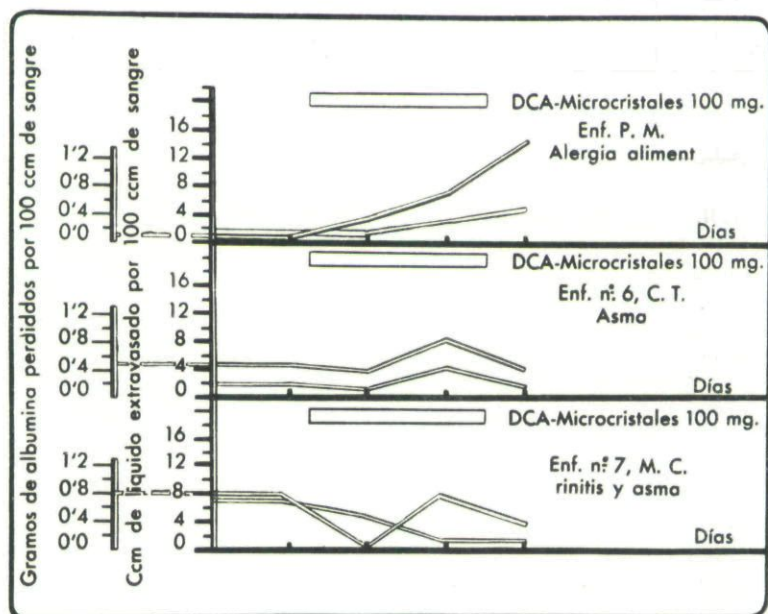


Fig. 1.

Variations on the proteins content and fluid that escape through the capillary wall on three patients studied above.

meter, studied capillary permeability, finding it increased in the areas of inflammation or papules produced by histamine, but *Criep* and *Levine* (31) do not, by means of the dermo-fluorometer, find any appreciable difference between normal and allergic individuals, some of them with urticaria.

Hermann and *Kanof* (32) do not find any differences either between the intensity of the colouring of the allergic papule or histaminic one in normal or allergic individuals, by means of the dermo-fluorometer.

EXPERIMENTAL PART

The extremely scarce literature on capillary permeability in allergic individuals in opposition to its supposed importance, together with the in-conclusive action of corticoids upon per-

TABLE I

Values of Proteins (p in grams) & Liquids (L in c.c.) that escape from the capillaries before, during and after a treatment with DCA and cortisone.

Ref. no.	Name and diagnosis	Class prepared and daily dosis	No. of days treatment	Values before		Values during		Values after	
				L	P	L	P	L	P
1	E. R.	DCA microcryst 100 mg.	3	7	0.4	4	1.6		
2	P. M.	DCA microcryst 100 mg.	3	1	0.3	1	0.4	3	0.5
3	V. B. rhinitis & asthma	DCA microcryst 100 mg.	2	1	0.4	2	0	3	0
4	J. F. asthma	cortisone	2	2	0.4	2	0.4		
5	R. C. urticaria	DCA 90 mg. 1st day sol aqueous 2nd & 3rd day microcrystals 100 mg.	3	1	0.3	1	0.4		
6	C. T. asthma	DCA 90 mg.	3	2	0.5	1	0.4		
7	M. C. asthma	DCA 90 mg.	3	7	0.8	3	0	2	0.5
8	E. C. asthma	cortisone 100 mg.	5	0	0	1	0.8	1	0.4
						2	0.4		
						0	0		
						3	0.2		
						2	0		
						2	0		
						5	0	3	0
9	M. R. asthma	DCA microcryst 100 mg.	2	2	0.4	8	0.8	1	0.7
10	F. B. asthma	cortisone 100 mg.	5	3	0.7	3	0.7		
						1	0.3		
						2	0.7	1	0.3
11	A. O. asthma	cortisone 100 mg.	5	1	0.8	1	0.4		
						0	0.3		
						1	0.7		
						1	1		
12	F. R. rhinitis & asthma	—	—	1	0.4				
				2	1.4	—	—	—	
				1	0.5				
13	J. B. urticaria	—		0	0.5				
				0	0	—	—	—	
14	A. S. asthma	—		0	0.3				
				0	0	—	—	—	
15	T. C. asthma	—		3	0	—	—	—	
16	R. G. asthma	DCA 100 mg.	3	4	0.3				
				2	0.3	—	—	—	
				2	0.7				

meability, has induced us, as we have stated at the beginning of this communication, to study: 1°— the conduct of capillary permeability in allergic individuals: 2°—. Its modification under the action of the corticoids DCA and cortisone¹.

TECHNIQUE

The study of capillary permeability has been carried out using the technique of *Landis* (33) to which we refer the reader for details.

The results of the experiments are shown in Table I.

CONCLUSIONS

Our work has enabled us to come to the following conclusions:

1°—We have been able to observe in the small number of patients studied, that in nearly all of them there exists an abnormal passing of proteins because of the experimental venous stasis.

2°—On the other hand, the passing of the liquid occasioned by that stasis is normal.

It cannot be said, therefore, that allergic patients present an altered capillary permeability, but only a greater protein permeability.

3°—In some of the patients, not treated with DCA or cortisone, and studied as controls, it could be observed that the values of capillary permeability varied in a spontaneous way from one day to another.

4°—From this it may be inferred that not all oscillations observed when using DCA and cortisone must be attributed to the action of these hormones.

5°—Given the small number of patients that could be observed, but in whom experiments however continue, it is not possible to come to any conclusion whatsoever on capillary

¹ The drug used in these experiments have been *Altercortian* and *Altesona*, kindly provided by Laboratorios Alter, S. A. Madrid.

permeability being altered by the influence of DCA or Cortisone.

6°—Nevertheless it appears that DCA increases capillary permeability.

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